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Short communication

Illness history: Not associated with remission during treatment of major depression in 515 mood disorder patients

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ABSTRACT

Background: There is suggestive evidence that prior illness history may have little association with response to long-term treatment in bipolar disorder (BD) or recurrent major depressive disorder (MDD), but relationships of illness-history to treatment-response in acute episodes of depression require further testing.

Methods: We tested for associations of selected measures of illness history with remission during treatment of an acute index episode of major depression in 515 mood-disorder patients (327 MDD, 188 BD), using bivariate and multivariate methods.

Results: Remission of depression was more likely with lesser initial symptom-severity and bipolar diagnosis, but *not* related to years since illness-onset, previous depressions or episodes (based on counts, yearly rates, or %-of months ill), or other indices of illness-severity (hospitalization, co-morbidity, suicide attempt).

Conclusions: Likelihood of response to standard treatments for acute major depressive episodes in MDD or BD appeared to be largely independent of prior illness-history.

1. Introduction

Unipolar depressive and bipolar major mood disorders are leading causes of the worldwide burden of disease and disability (Ferrari et al., 2013; Murray and Lopez, 1996; WHO, 2012). In addition to morbidity, disability, and high direct and indirect costs, major depressive illness is associated with increased mortality due to suicide and to co-morbid cardiovascular, endocrine, pulmonary, and other diseases (Almeida et al., 2014; Miller et al., 2014; Osby et al., 2001; Schaffer et al., 2015; Tondo et al., 2007). Despite advances in modern psychiatric therapeutics, and availability of acceptably effective and safe antidepressant, antimanic, and mood-stabilizing medicines (Baldessarini, 2013), the long-term impact of treatment on depressive morbidity in all types of major mood disorders remains surprisingly limited (Forte et al., 2015), making prediction of response especially important.

In order to improve clinical treatment and to predict and enhance response and remission, there have been many attempts to identify clinical or biological features that predict responses to treatment of depressive illness. Several clinical predictors of short-term response have been proposed. They include relatively older age at onset, fewer years of illness, fewer episodes, less time in a current episode, and certain clinical subtypes (Arnow et al., 2015; Bagby et al., 2002; Kemp et al., 2008; Papakostas and Fava, 2008). In addition, some but not all studies have found that symptomatically more severe current depression and such clinical features as psychosis or severe melancholia, or co-morbid anxiety, substance-abuse, or medical disorders were associated with lesser responses to antidepressants (Arnow et al., 2015; Bagby et al., 2002; Pacchiarotti et al., 2011, 2013; Peselow et al., 1992). However, most of these factors have been inconsistent and insufficiently predictive to guide clinical treatment reliably (Bagby et al., 2002; Kemp et al., 2008; Papakostas and Fava, 2008). Alternative approaches to predicting response to treatment of depression include a growing range of psychometric, genetic, neuroimaging, and other biological measures, many of which are promising but still in development (Fabbri et al., 2014; Gudayol-Ferré et al., 2013; Kennedy et al., 2012; Olbrich and Arns, 2013; Phillips et al., 2015). In short, it remains uncertain whether the severity of past affective illness may tend to limit treatment-response.

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Our previous studies include evidence that even extreme differences in latency to mood-stabilizing treatments or the number of previous episodes did not affect responses to a variety of such treatments among large numbers of patients with bipolar disorder (BD) or recurrent major depressive disorder (MDD) (Viguera et al., 1998; Baethge et al., 2003; Bratti et al., 2003). In addition, more previous episodes of depression inconsistently predicted earlier recurrence after discontinuing antidepressant treatment (Viguera et al., 1998; Baldessarini et al., 2010).

The lack of consistent and compelling evidence concerning potential clinical predictors of short-term response to treatments for major depressive episodes in unipolar MDD or in BD, led us to test for associations of indices of prior affective morbidity and responses to treatment for acute major depressive episodes. Since cited previous findings suggested that prior morbid history had little effect on response to treatment in mood disorder patients, we hypothesized that past history of affective morbidity would have little effect on rates of remission in either BD or MDD patients treated for acute major depressive episodes.

2. Methods

2.1. Subjects

We analyzed information from systematically collected and recorded clinical assessments of consecutive adult patients with a major depressive episode associated with diagnoses of bipolar-I (BD-I), bipolar-II (BD-II), or unipolar MDD, treated between 1976 and May 2015. Subjects were evaluated, treated, and followed at the Lucio Bini Mood Disorders Center in Cagliari, Sardinia. Diagnoses were updated to meet DSM-IV-TR criteria after 2000, through 2015. All subjects underwent initial diagnostic assessments, treatment, and repeated follow-up evaluations by the same mood-disorders expert (LT), based on semi-structured interviews that followed the mood-disorder components of SCID-I research assessment procedures, as well as extensive, prospective, follow-up clinical assessments, typically every 2–4 weeks for three months, and every 2–3 months thereafter, with construction of life-charts in use at Lucio Bini Center since the 1970s. In addition, all subjects were rated for severity of depressive symptoms with the 21-item Hamilton Depression Rating Scale ($HDRS_{21}$) at intake (with a required initial total score of ≥ 18 for inclusion) and at least once thereafter, including to support clinical impressions of remission from index depressive episodes within six months. Initial hypomanic symptoms were ruled out clinically and by routine use of the Young Mania Rating Scale (YMRS). Remission was defined as reaching an $HDRS_{21}$ score of ≤ 7. The maximum of six months was imposed to limit effects of spontaneous remission; subjects who did not reach remission or became hypomanic by DSM-IV criteria before six months from the start of treatment were considered "nonremitters" for this study. Depressed patients with more than three hypomanic symptoms or severe agitation at intake were excluded to avoid potential induction of pathologically elevated mood by antidepressant treatment (Pacchiarotti et al., 2013; Tondo et al., 2010).

All subjects provided written, informed consent for data collection to be analyzed and presented anonymously in aggregate form, following approval of a local ethical review board. Data-management complied with US federal Health Insurance Portability and Accountability Act (HIPAA) regulations pertaining to confidentiality of patient records. Required data were entered into a computerized database (by CV and LT), coded to protect subject identity; all authors participated in data-analysis, literature searching, and reporting.

2.2. Treatment

Treatment was determined clinically and was flexible and individualized, as reported previously (Tondo et al., 2013). Antidepressant drugs employed included modern agents (serotonin reuptake-inhibitors, or the serotonin-norepinephrine reuptake-inhibitors duloxetine or venlafaxine), or older drugs (tricyclics, maprotiline, mianserin, or the monoamine oxidase-inhibitor tranylcypromine). In addition to antidepressants, a mood-stabilizing or antipsychotic drug could be added. Mood-stabilizers included lithium carbonate or carbamazepine, lamotrigine or sodium valproate; antipsychotics included atypical agents (aripiprazole, olanzapine, or quetiapine) in moderate doses. Use of sedatives and medically required treatments was held constant for at least six months.

2.3. Study design

The primary study-aim was to test the hypothesis that more previous morbidity or years of illness would not lead to reduced rates of achieving clinical remission from a newly treated, acute episode of major depression within six months in both MDD and BD cases. Primary consideration was given to the following indices of clinically, retrospectively assessed, past depressive morbidity: [a] number of depressive episodes, [b] mean estimated rate of depressions per year since illness-onset, [c] years from estimated age at illness-onset to clinic-intake; and [d] the approximate proportion of months in depression per year since illness-onset. Secondarily, we also considered overall major affective morbidity (manias, hypomanias, and mixed-states as well as depression) assessing: [a] total number of affective episodes, [b] their rate per year, and [c] percentage of months since onset with affective illness. Additional covariates considered were: sex, age at illness-onset and at clinic-intake, marital status, having children, education at least through high school, employment (including housewives, students, and retired), diagnosis (BD vs. unipolar MDD), family history of mood disorders, type of first-lifetime mood episode, evidence of early physical or sexual abuse or trauma, general medical and psychiatric or substance-abuse co-morbidity, previous psychiatric hospitalization, suicide attempt, initial $HDRS_{21}$ score, and types of treatments in the index episode of depression.

2.4. Data analysis

Three authors (LT, GHV, RJB) compared descriptive factors, selected *a priori*, to clinical outcomes between subjects who did or did not attain clinical remission of the index major depressive episode within six months, supported by final $HDRS_{21}$ scores of ≤ 7. Each subject was counted once, an evaluated at a first treated episode of depression at the study site. Comparisons of factor frequencies or values were based on contingency tables (χ^2) for categorical measures (degrees-of-freedom [df] = 1, except as noted) and ANOVA (*t*-score) for continuous variables. Factors of interest were then included in multivariate logistic regression modeling for associations with remission as the dependent variable, so as to provide Odds Ratios (ORs, with 95% confidence intervals [CIs]). Statistical analyses employed commercial digital programs (*Statview-5*®, SAS Institute, Cary, NC for data spreadsheets, and *Stata-12*®, StataCorp, College Station, TX for computations).

3. Results

The study sample consisted of 515 patients in an acute episode of major depression associated with diagnoses of major depressive